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PATENT  
Attorney Docket No.: A-60709/WH

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

|                       |   |                           |
|-----------------------|---|---------------------------|
| In re application of: | ) | Examiner: Dr E C Kemmerer |
|                       | ) |                           |
| W Godfrey et al.      | ) | Group Art Unit: 1812      |
|                       | ) |                           |
| Serial No. 08/147,784 | ) |                           |
|                       | ) |                           |
| Filed: 3 Nov 1993     | ) |                           |
|                       | ) |                           |
| For: Receptor on the  | ) |                           |
| Surface of Activated  | ) |                           |
| T-cells: ACT-4        | ) |                           |
|                       | ) |                           |
|                       | ) |                           |

CERTIFICATE OF MAILING

I hereby certify that this correspondence, including listed enclosures, is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, DC 20231 on April 27, 1995.

Signed:

*Maria Ciganovich*  
Maria Ciganovich

DECLARATION of Dr John G Shields pursuant to 37 C.F.R. §1.132

Commissioner of Patents  
and Trademarks  
Washington, DC 20231

Sir:

I, Dr John G Shields, do hereby declare as follows:

1: I am Vice President, Cell Sciences, at Cantab Pharmaceuticals Research Limited, of Cambridge, UK. I am familiar with the content of the patent application by Godfrey et al identified herein, and my qualifications and experience relevant to this matter include the following:

I graduated B.Sc with first class Honours in Immunology at Glasgow University, Scotland, in 1977. Later I was awarded the doctoral degree of PhD for research in immunology by the University of Glasgow in 1983/4. I have carried out

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research in immunology for a total of 18 years to date, including periods of research activity at the University of Glasgow, the University of London, UK, and the Glaxo Institute for Molecular Biology, Geneva, Switzerland; and I have held my present position mentioned above at Cantab Pharmaceuticals since 1992. I have authored or co-authored about 30 published papers in the field of immunology.

2: I am aware that there is substantial experience, in the field of cell- surface binding proteins, with the comparison between membrane proteins and corresponding isolated extracellular domains.

3: 'Extracellular domain' is a concept familiar to skilled workers in this field. The term 'extracellular domain' is for example referred to in a paper by J G Flanagan et al in Cell 63 (1990) pp 185-194 (examiner's citation S2 in the record of the present application): I see that no general explanation of the term is given in that paper, and that fact illustrates, I believe, that the meaning of the term is familiar enough so that explanation is unnecessary to the skilled reader.

4: Nevertheless, if anybody should be in doubt about it, the possibility of any doubt about the nature of an 'extracellular domain' would be in my view removed for any reader of Flanagan et al, because on page 186 of that paper, right col, second para, the extracellular domain is noted as 'ending immediately before the first hydrophobic aminoacid of the transmembrane region'. These are terms understood by those skilled in this art, and mean, in the context of the protein under discussion in the Flanagan et al paper, that the extracellular domain is that part of the given sequence that begins at the N-terminus and ends just before the transmembrane region.

5: I am aware that there has been experimental comparison, in the field of immunology, between the membrane-bound forms of a number of proteins and their isolated extracellular domains. In each case principal binding functions are

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known to be shared in common between the membrane bound form and the corresponding soluble extracellular domain. This is true for example for immunoglobulins, in respect of the soluble forms that are secreted by antibody-secreting B-cells and the corresponding membrane-bound forms found on the surfaces of such B cells. Examples of proteins for which corresponding membrane-bound forms and soluble extracellular domains are known include: leukocyte (B-cell) surface antigen CD40; CTLA4, a T-cell membrane protein that binds to co-stimulatory molecule B7; cell-surface binding protein ICAM-1; and others. In each case the extracellular domain retains its ligand-binding properties and antigenic character when expressed in soluble form without the transmembrane region.

6: I am sure that a person of ordinary skill in this field would expect the same if confronted with an extracellular domain corresponding to a new binding protein which is of the membrane bound type 1. 'Membrane bound type 1' denotes a protein in which there is a transmembrane region in the aminoacid sequence, identifiable by the hydrophobicity due to its aminoacid residues, and in such a protein the portion of the aminoacid sequence between the N-terminal and the transmembrane region encodes an extracellular domain with a binding function or other extracellular functionality.

7: The nucleotide sequence and deduced aminoacid sequence of ACT-4 in the present patent application indicates that ACT-4 is recognizable to those skilled in the field as a member of the membrane-bound type 1 group of proteins. (The same is also true of the protein under discussion in the Flanagan et al paper cited in paragraph 3 above.) Accordingly I am sure that it would be generally expected, given the knowledge imparted by the specification here, that ACT-4 and the extracellular domain corresponding to ACT-4 would share principal binding functionality and antigenic character.

8: In particular relation to ACT-4, I note that Figure 5 in the drawings of the patent application clearly shows a sequence that those skilled in this art would take with high probability to be a transmembrane segment, (as mentioned on page 49, lines 33-36) i.e. starting at the aa residue encoded by nucleotide bases at sequence number 655 in the drawing. It would be clear to the reader (e.g. from page 49 line 36) that one form of an extracellular domain can be obtained by using the sequence that remains if the entire aminoacid sequence is truncated to remove the transmembrane region, i.e. the extracellular domain is what extends from the mature-protein N-terminus coded from about base residue 88, onwards, and ending immediately before the transmembrane region. It would be understood by those skilled in the art that the extracellular domain can extend shorter or longer without making an appreciable functional difference. In particular, I would expect it possible to make no appreciable functional difference by having a sequence shorter or longer by a few aminoacids relative to the example of extracellular domain sequence derived as described above.

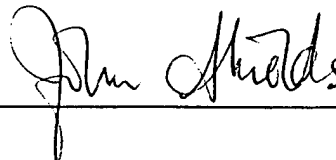
9: In addition to the considerations outlined in the immediately preceding paragraphs, an experiment has in fact been carried out successfully in my laboratory at Cantab Pharmaceuticals Research Limited, at Cambridge, UK. That experiment has shown that an isolated extracellular domain of ACT-4, prepared as a recombinant protein fused to a further soluble amino-acid sequence, possesses shared principal binding functionality with the cell-associated ACT-4, i.e. it has been found to bind to cells expressing surface-associated gp34 protein. Surface-associated gp34 protein is now known to be a physiological binding partner for ACT-4. This verifies experimentally that a soluble protein comprising the extracellular domain of ACT-4 has shared binding functionality with the entire protein.

10: I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that the

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making of willful false statements and the like is punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or of any patent issued thereon.

Date: 13.4.95

A handwritten signature in cursive script, appearing to read "John G. Shields", written over a horizontal line.

Dr John G Shields  
Vice President, Cell Sciences  
Cantab Pharmaceuticals Research Limited  
184 Cambridge Science Park  
Milton Road, Cambridge, UK



# American Type Culture Collection

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## BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

### INTERNATIONAL FORM

#### RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3 AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

Becton Dickinson & Company  
Attention: V. Maino  
2350 Qume Drive  
San Jose, CA 95131

Deposited on Behalf of: Becton Dickinson & Company

Identification Reference by Depositor:

ATCC Designation

Hybridoma cell line, L106

HB 11483

The deposit was accompanied by: \_\_\_ a scientific description \_\_\_ a proposed taxonomic description indicated above.

The deposit was received November 3, 1993 by this International Depository Authority and has been accepted.

#### AT YOUR REQUEST:

☒ We will inform you of requests for the strain for 30 years.

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If the culture should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace it with living culture of the same.

The strain will be maintained for a period of at least 30 years after the date of deposit, and for a period of at least five years after the most recent request for a sample. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the culture cited above was tested November 5, 1993. On that date, the culture was viable.

International Depository Authority: American Type Culture Collection, Rockville, Md. 20852 USA

Signature of person having authority to represent ATCC:

Bobbie A. Brandon

Date: November 5, 1993

Bobbie A. Brandon, Head, ATCC Patent Depository

cc: Robert M. Hallenbeck

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